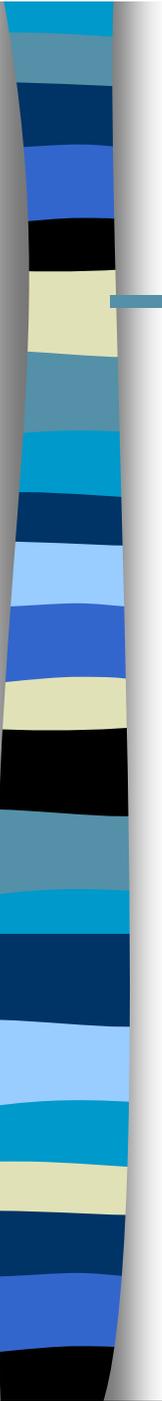


# Allergic Inflammation in Infant/Preschool Wheezing

Marzena E. Krawiec M.D.  
Associate Professor of Pediatrics  
Section Head Pulmonary Medicine

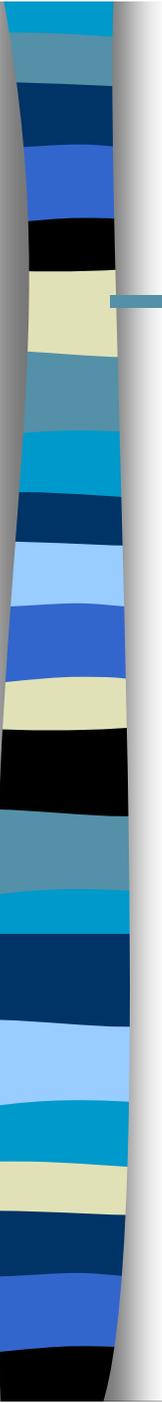




# Disclosures

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- Speaker's Bureau: Aerocrine



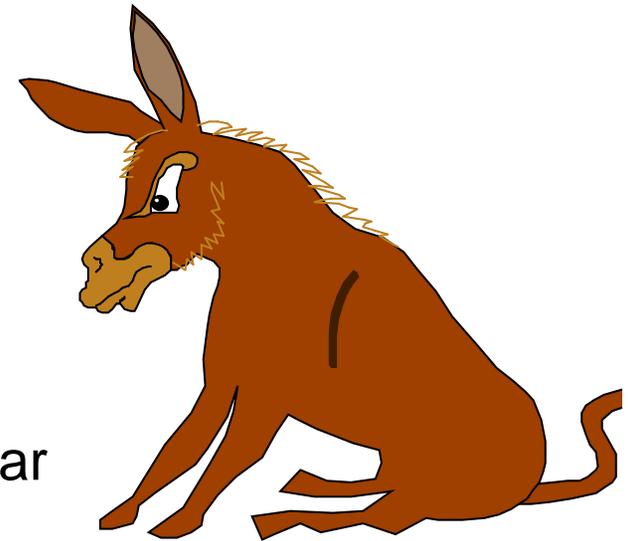
# KEY OBJECTIVES:

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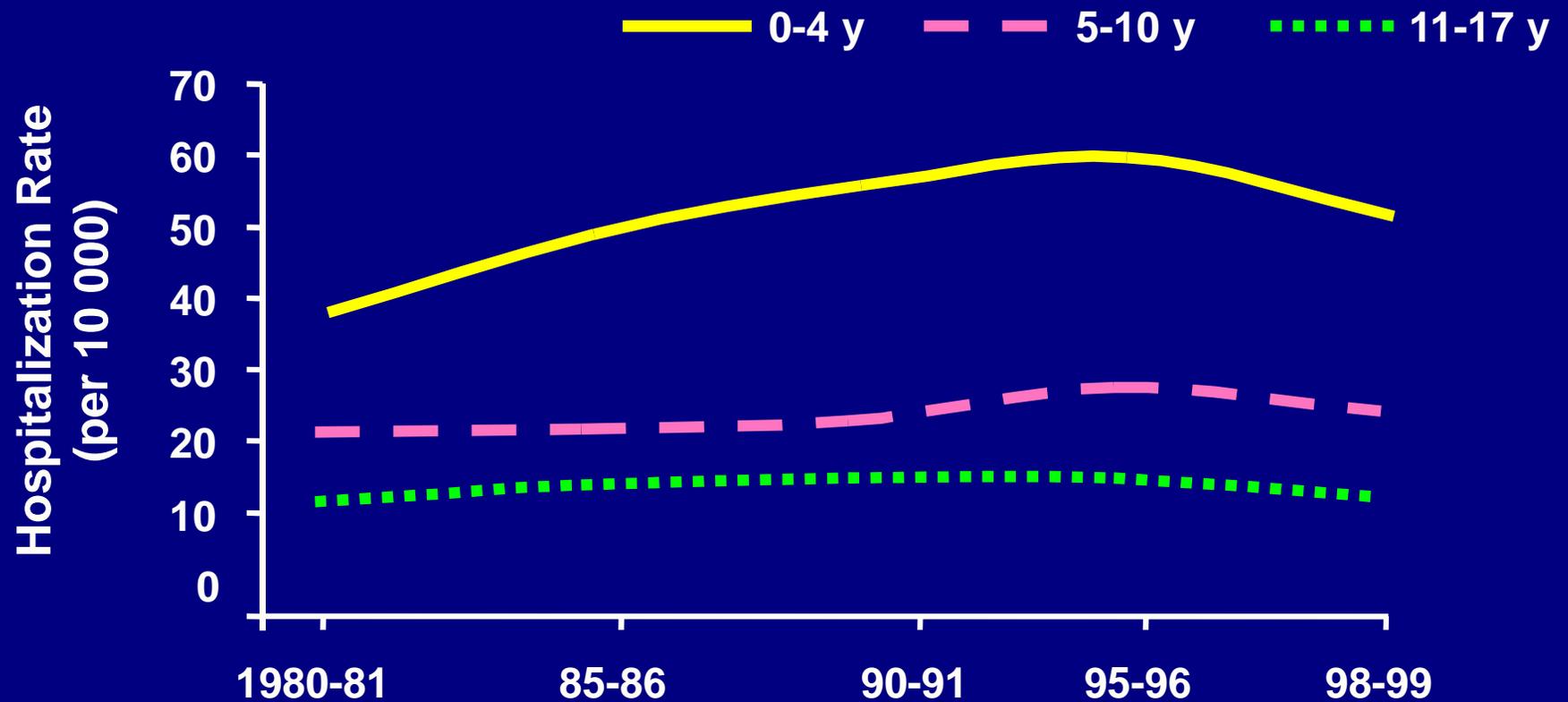
- Review the unique characteristics of infancy and the infant airway predisposing to wheezing
- Review the phenotypic presentations of early childhood wheezing
- Recognize the importance of atopy and early infection in the development of persistent wheezing
- Identify biomarkers which may distinguish transient from persistent wheezing children

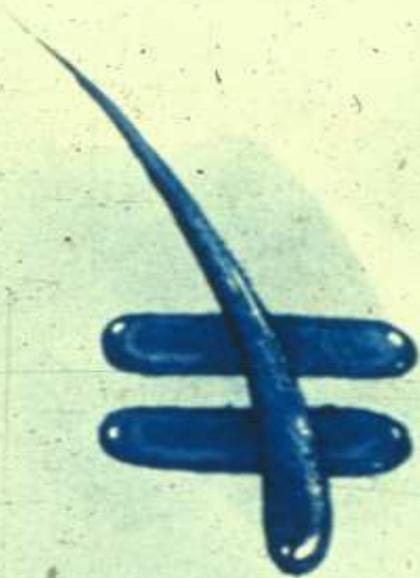
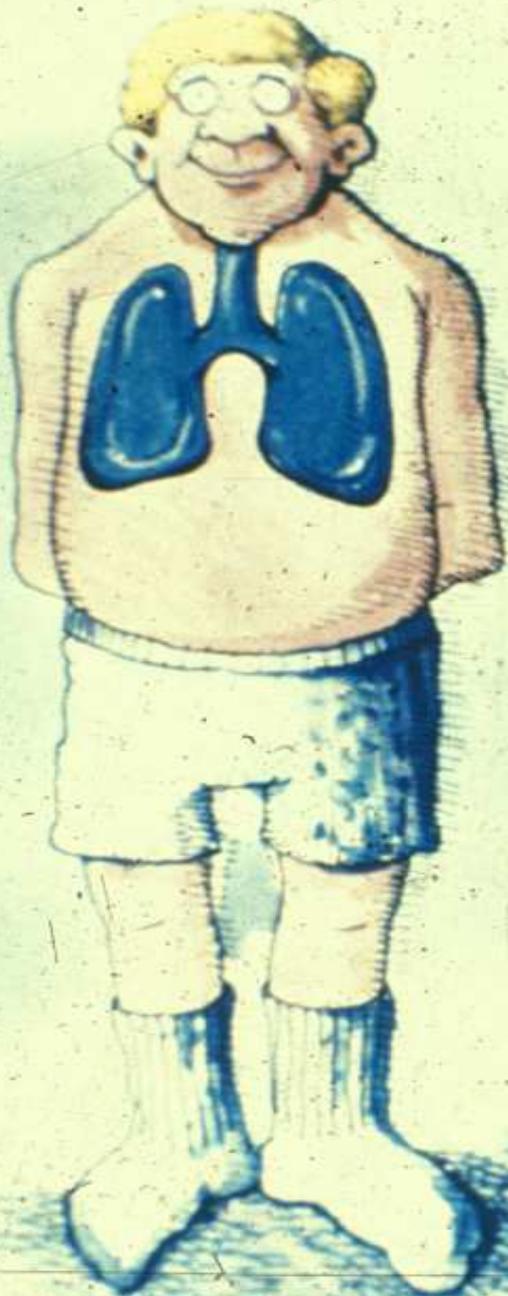
# The Nature of the Beast

- **Most common chronic illness in childhood**
  - 87% had unscheduled physician visits in
  - the year prior to hospitalization
- **#1 chronic illness causing school absences**
  - 3X the school absences of children without asthma
- **78% of parents report a negative impact on the entire family**
  - 40% of patients have sleep disturbance
  - 1-2 nights/week
  - 36% of parents reported missing work due to their child's asthma in the prior year



# Hospitalizations Due to Asthma in Children





# Pathophysiologic Properties Predisposing Infants and Young Children to Wheeze

1. ↓↓ Bronchial smooth muscle content
2. Hyperplasia of bronchial mucous glands
3. ↓↓ radius of conducting airways
4. ↑↑ peripheral airway resistance due to ↓↓ size
5. ↑↑ Chest wall compliance
6. Diaphragm
  - Horizontal insertion of the diaphragm to the rib cage
  - ↓↓ number of fatigue-resistant skeletal muscle fibers
7. Deficient collateral ventilation

# Bronchoconstriction

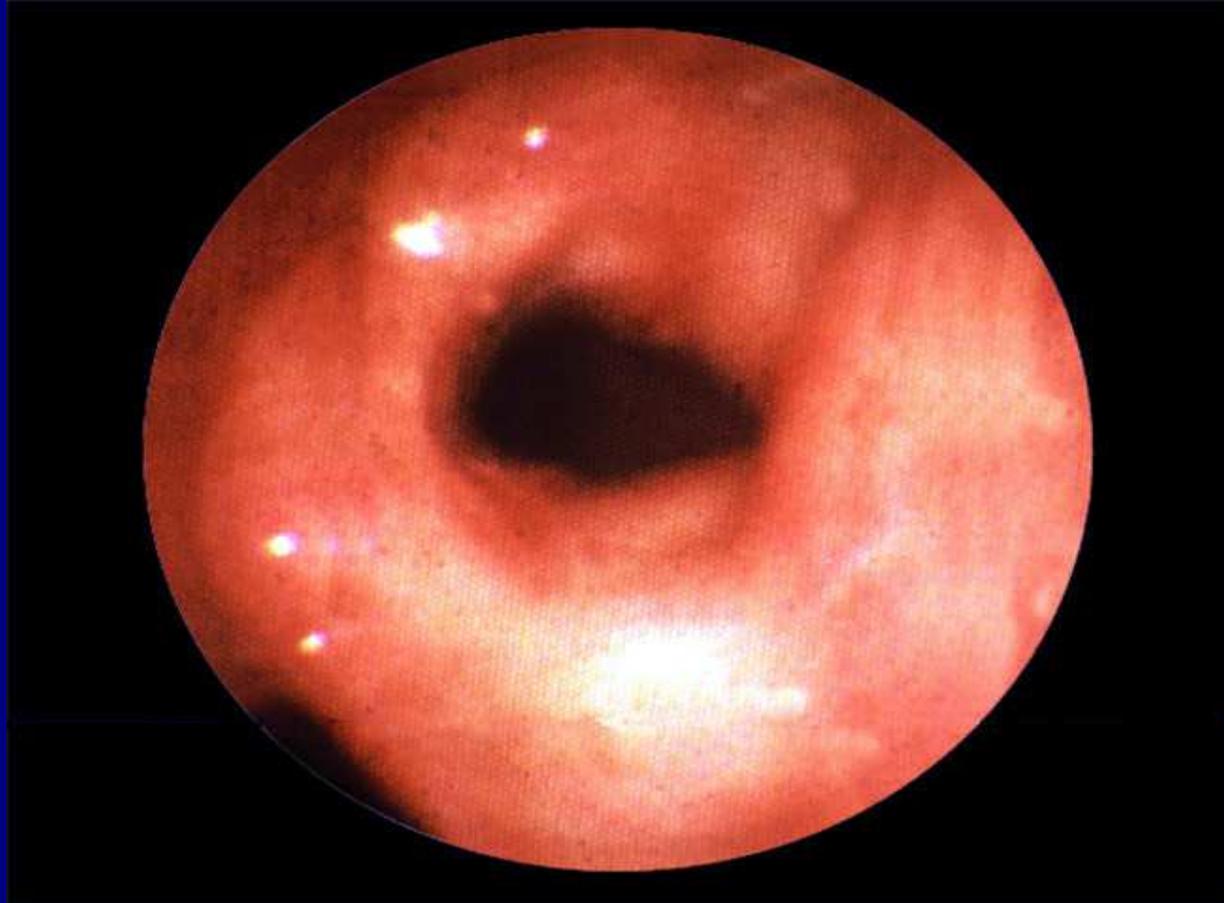


**Before**

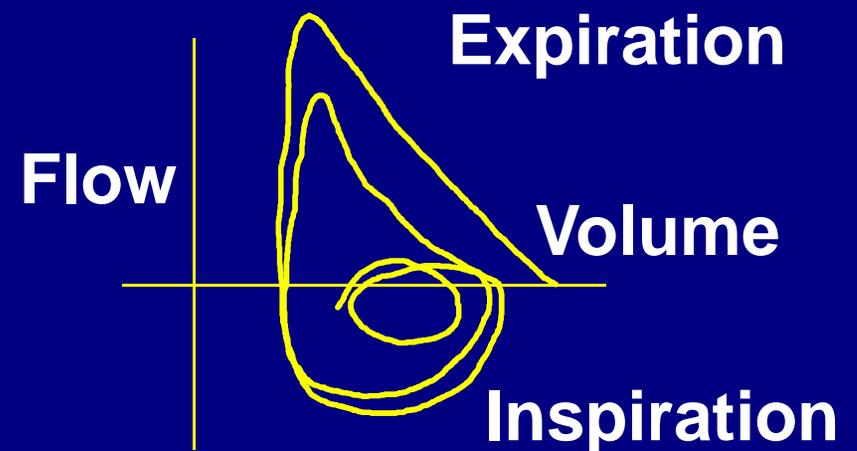
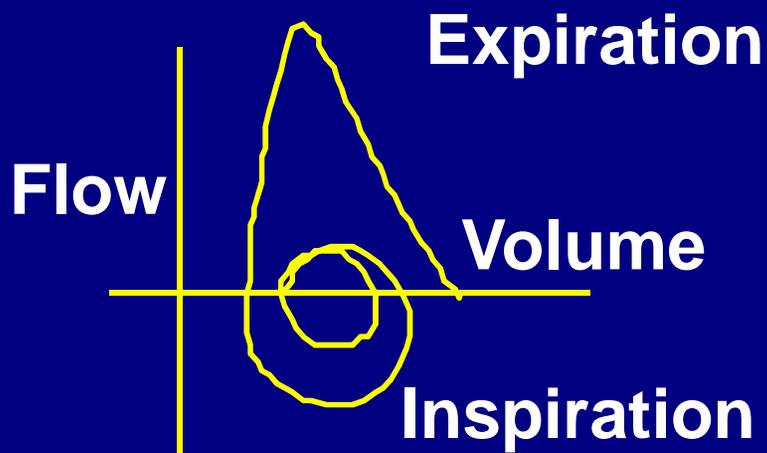


**10 Minutes After  
Allergen Challenge**

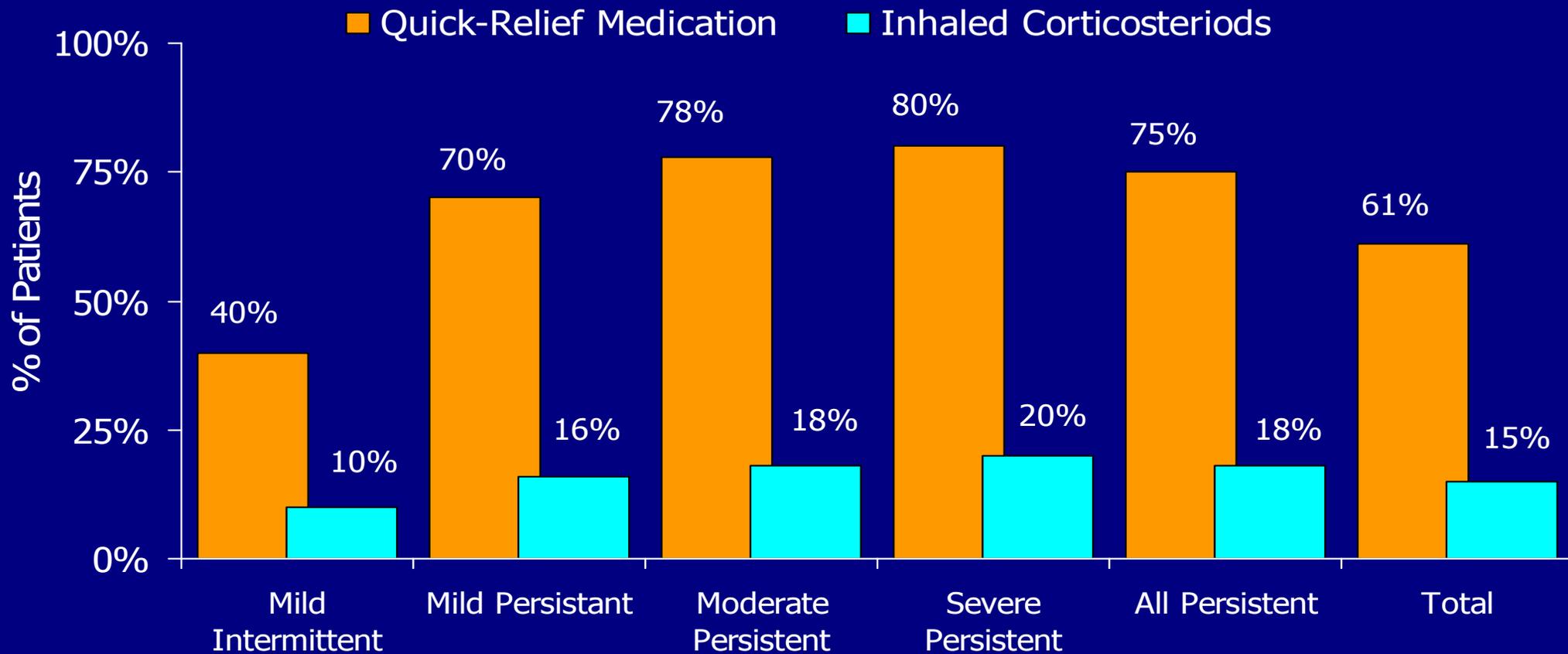
# Airway Mucosal Edema

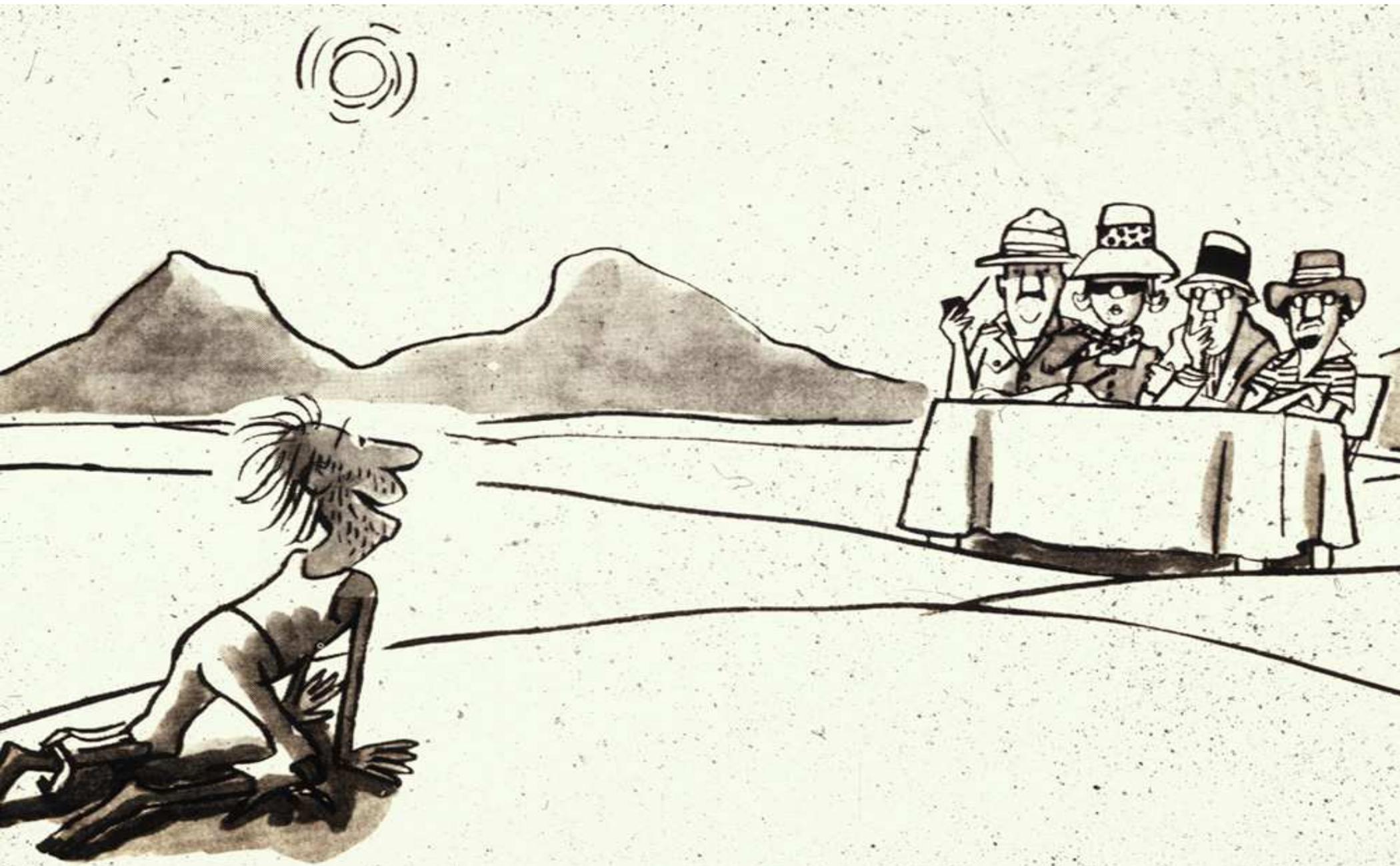


# Airway Remodeling



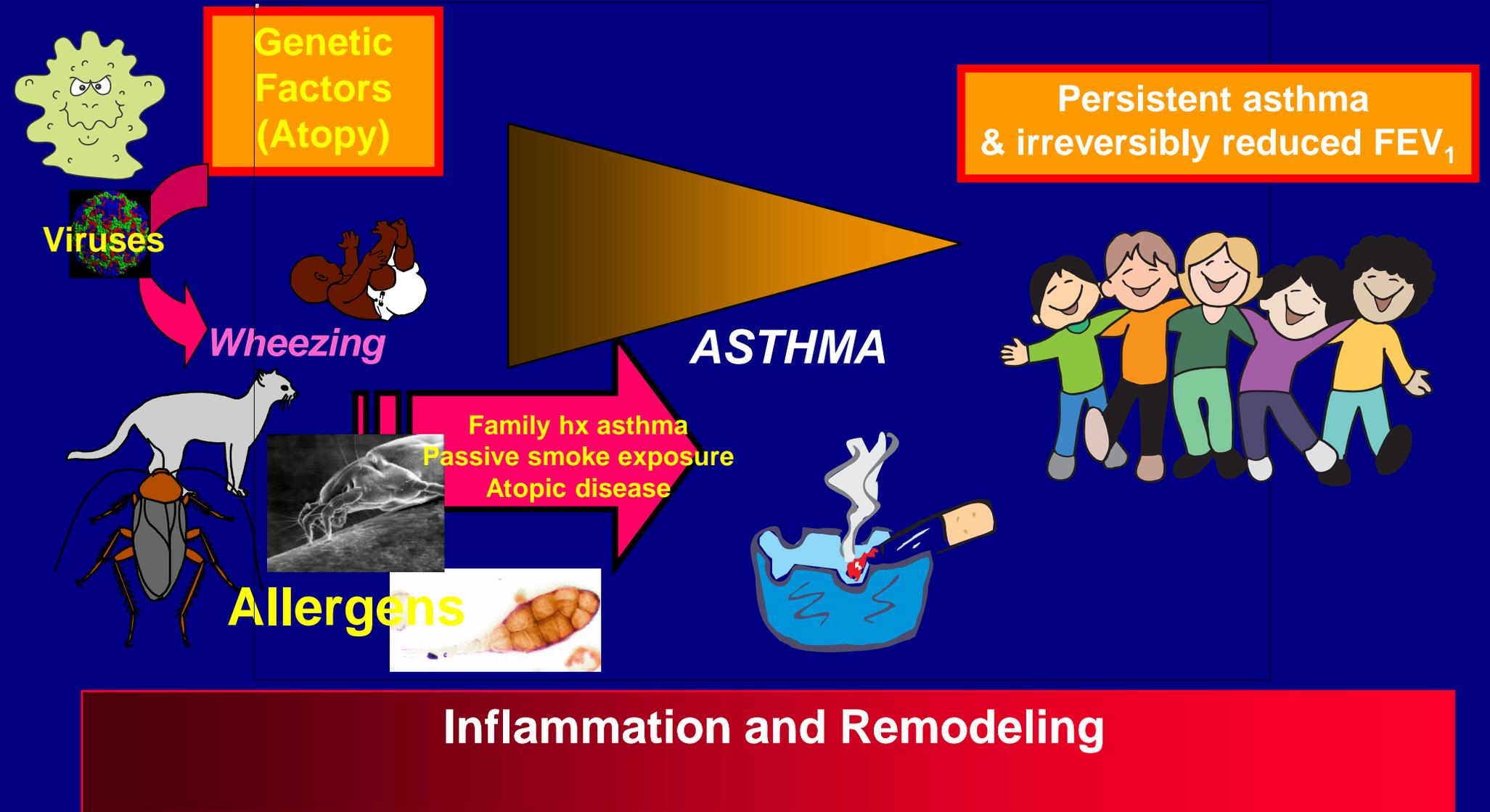
# Medication Use and Asthma Severity



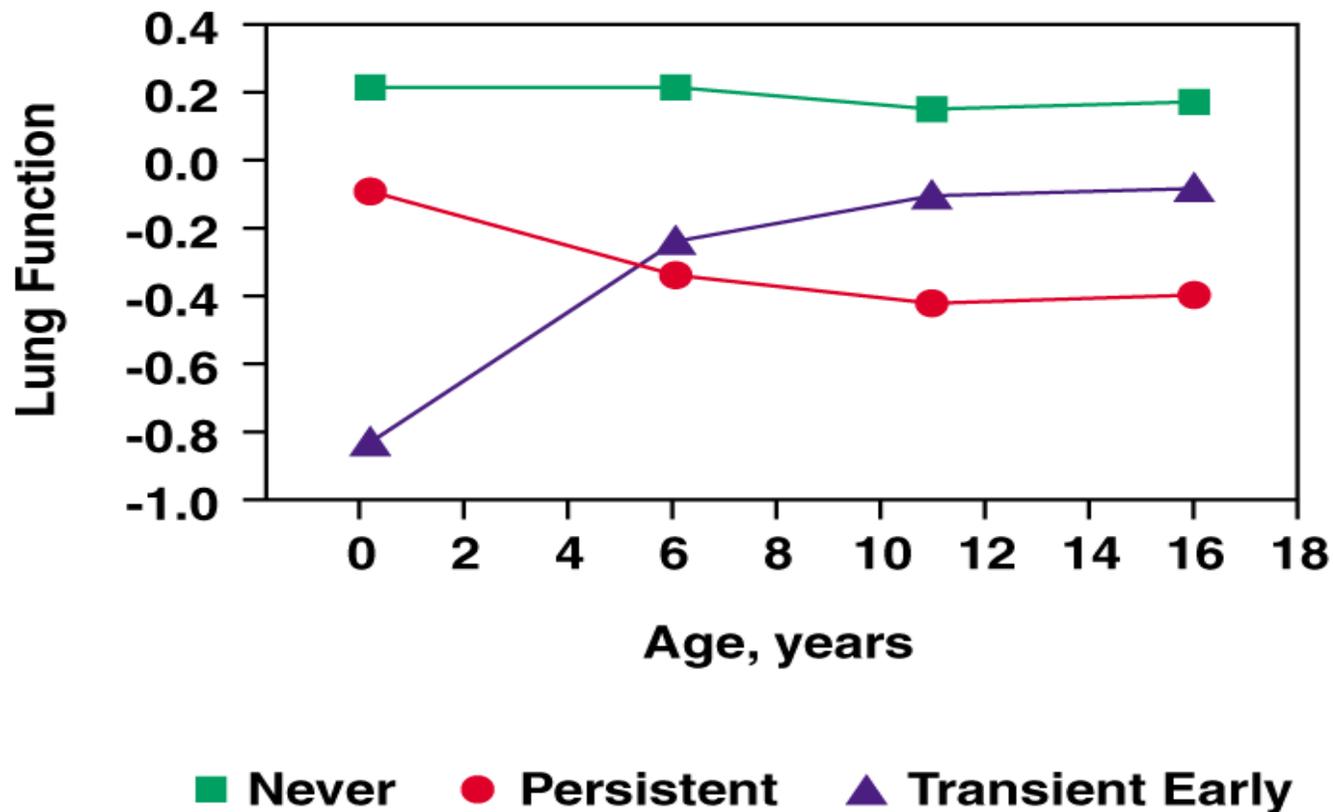


*"Thank God! A panel of experts!"*

# The Natural History of Asthma



# Longitudinal Evaluation of Lung Function in Wheezing Infants



Martinez FD et al. *NEJM* 332:133, 1995

# Infant Wheezing: Phenotypes

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- **Distinguishing factors:**
  - **Atopy**
  - **Airway Hyperresponsiveness**
  - **Lung Function**

# Asthma Predictive Index

– H/o  $\geq 4$  wheezing episodes in the past year  
(at least one must be MD diagnosed)

**PLUS**

– One major criteria or -Two minor criteria

- Parent with asthma

- Atopic dermatitis

- Aeroallergen  
sensitivity

- Food sensitivity

- Peripheral eosinophilia ( $\geq 4\%$ )

- Wheezing not related to  
infection

*If +, then 65% likelihood of developing clinical asthma*

*If -, then 95% likelihood of not developing clinical asthma*

Modified from: Castro-Rodriguez, AJRRCM, 2000.

# Eczema at 2 years of age



# Child with chronic cough With Positive Skin Test Reactions to Common Aeroallergens



# Infantile Wheeze - AHR

- **Infants are born with highly responsive airways becoming less so with age**
  - Factors such as parental smoking, respiratory illness and/or allergen exposure predispose infants to airway narrowing and potential decline in lung function.
  - These factors may interfere with the natural decline in airway hyperresponsiveness with age progression.

# Transient Early Wheezing

- Characterized by recurrent episodes of wheezing in the first year of life
  - Resolution of symptoms between ages 3-5 years<sup>1</sup>
- Most prevalent form of early wheezing
  - Almost 60% of subjects who wheezed in TCRS had resolution of their symptoms by age 6<sup>1</sup>
- No significant relationship to atopy<sup>1,2</sup>

<sup>1</sup>Martinez FD, et al. N Engl J Med 1995; 332: 133-8.

<sup>2</sup>Kurukulaaratchy RJ, et al. Clin Exp Allergy 2003; 33: 573-78.

# Transient Wheezers

- **Risk factors:**

- **Maternal smoking during pregnancy**

- Only significant variable associated in TCRS (OR 2.2 [95% CI 1.3-3.7])<sup>1</sup>
- Italian Studies of Respiratory Disorders in Childhood and the Environment (SIDRIA; OR 1.46 [95% CI 1.26-1.69])<sup>2</sup>
- Swedish BAMSE cohort (4089 infants); OR 2.1 [95% CI 1.2-3.7]<sup>3</sup>

- **Lower level of lung function in infancy before any respiratory infections<sup>4</sup>**

<sup>1</sup>Stein RT, et al. Am J Epidemiol 1999; 149: 1030-7.

<sup>2</sup>Rusconi F, et al. Am J Respir Crit Care Med 1999; 160: 1617-22.

<sup>3</sup>Lannero E et al. Respir Res 2006; 7:3.

<sup>4</sup>Martinez FD, et al. N Engl J Med 1995; 332: 133-8.

# The Effects of Atopy

# Perennial Allergen Sensitization Early in Life & Chronic Asthma In Children

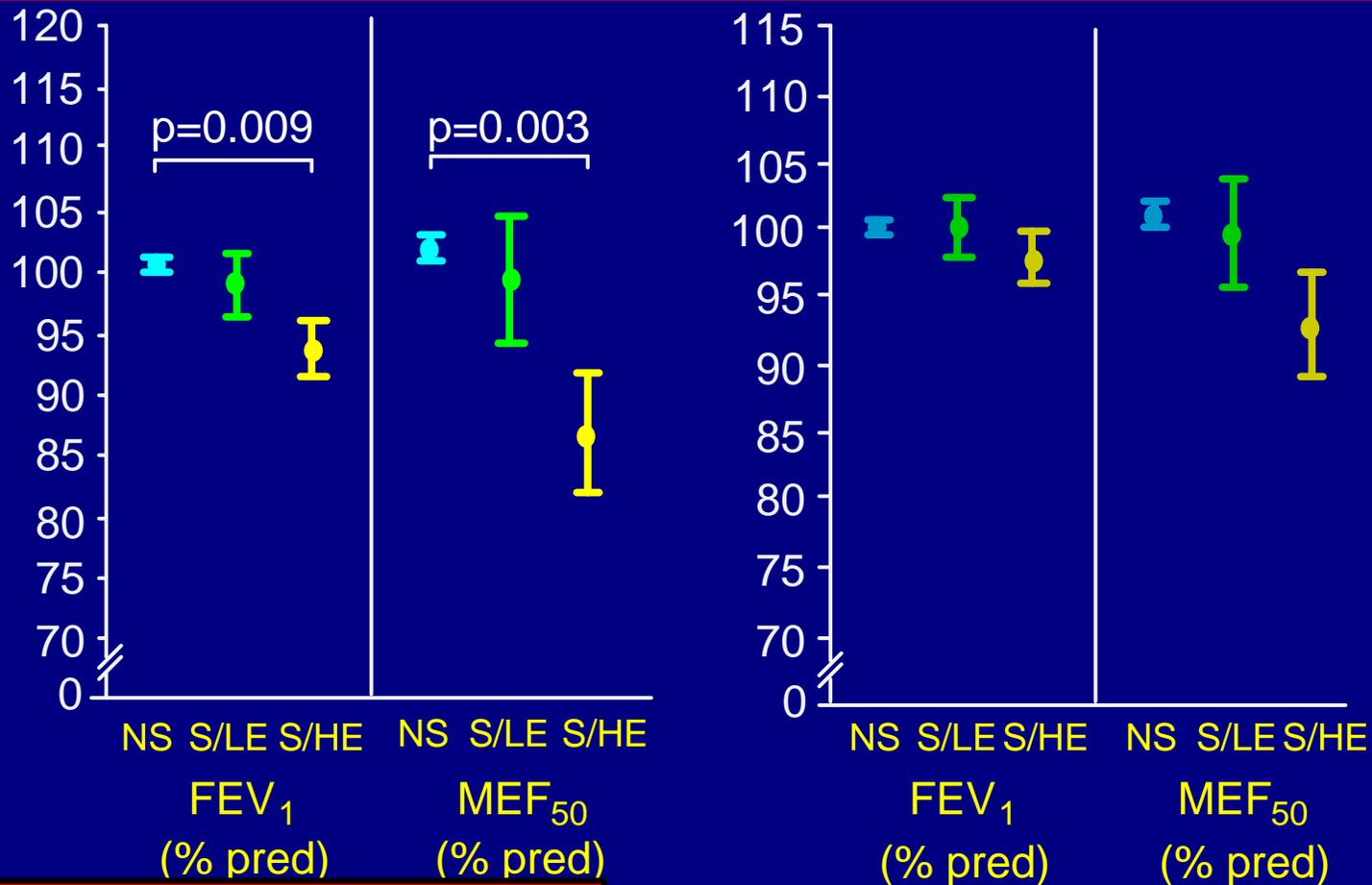
- **German Multicenter Allergy Study (MAS)**

- birth cohort of 1314 children
- followed from birth to 13 yrs
  - Sensitization measured at 1,2,3,5,6,7, &10 yrs;
  - Allergen exposure at 6 &18 mo, 3, 4, 5 yrs;
  - Lung function at 7, 10, 13 yrs.

- **Results:**

- 90% with recurrent wheeze but not atopic had lost their symptoms at school age and had normal lung function at 13yrs
- 56% atopic wheezers had active asthma at 13 yrs.
- Sensitization to indoor allergens  $\leq 3$  yrs associated with impaired lung function

# Time of Sensitization and Degree of Exposure Determines Degree of Lung Function Impairment at 7 yrs



Illi et al., *Lancet* 2006; 368:763-70.

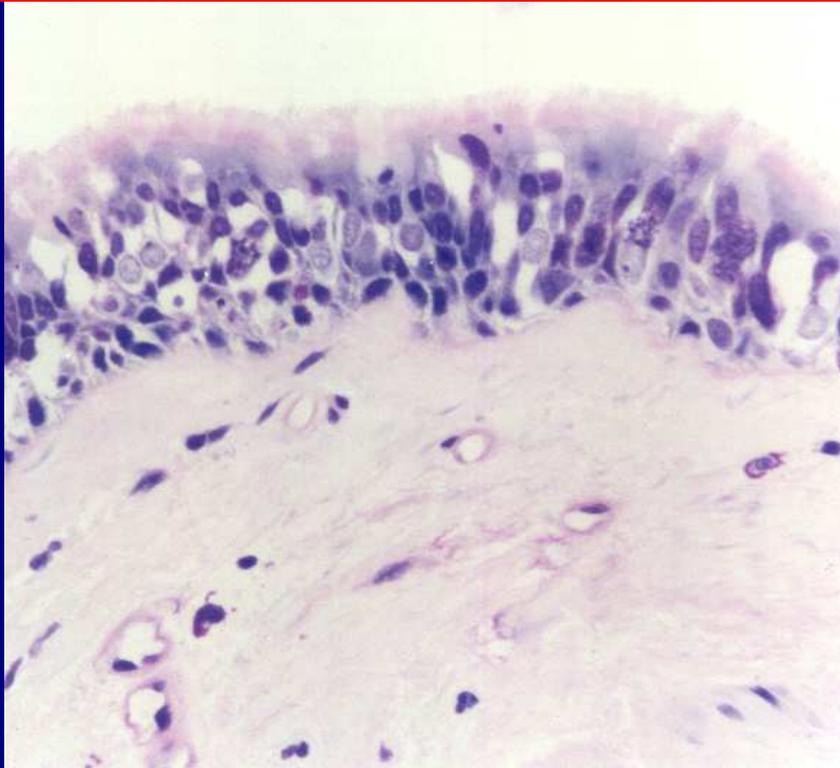
# Biomarkers of Inflammation

# Asthma Histopathology in Children

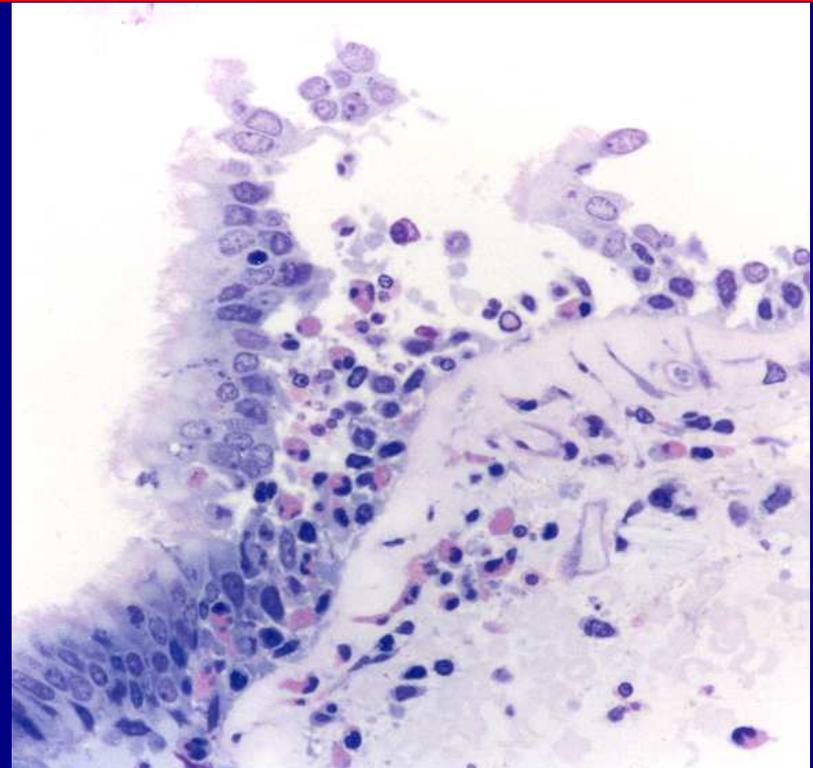
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- **Lung biopsies** from 2 children with asthma in remission compared to 2 children dying in status
  - *Similar:* Goblet cell hyperplasia, mucus plugging, collagen deposition
  - *Different:* In status, larger numbers of submucosal eosinophils and more extensive denudation of the epithelium

# Bronchial Biopsy From Subjects With and Without Asthma



Normal



Asthma

**Slide 27**

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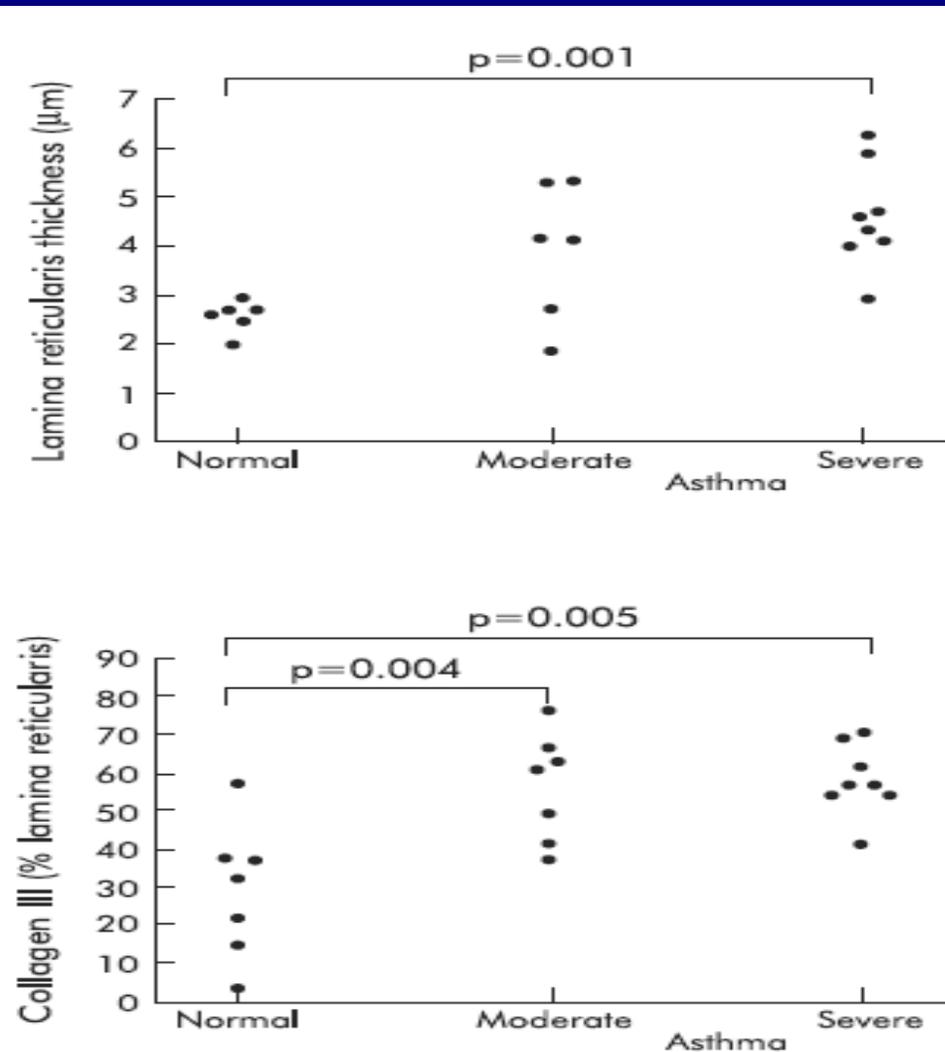
**JM4**

Add EM slide of patient with asthma

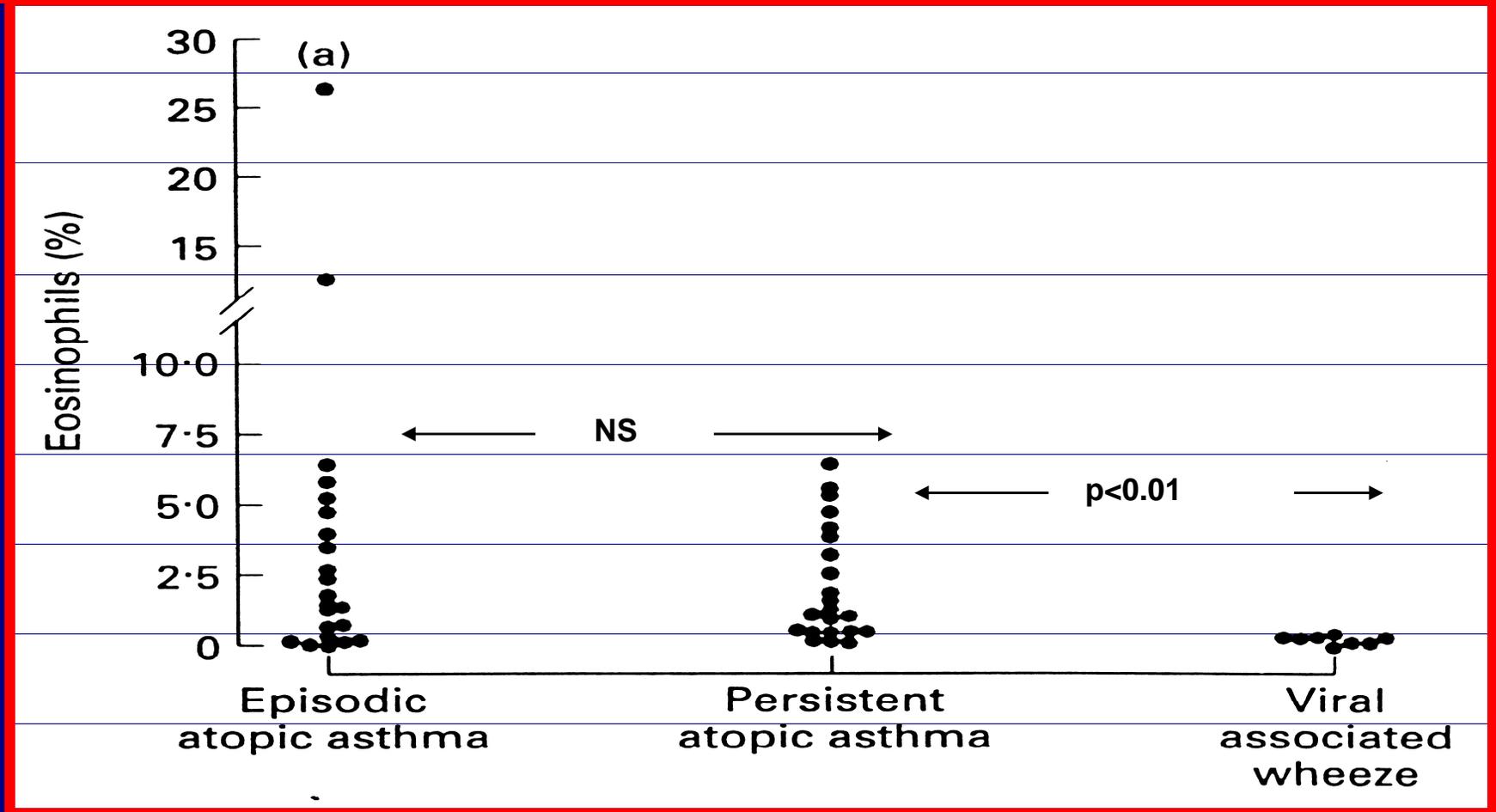
Jonathan Malka, 5/9/2009

# The Epithelium and Pediatric Asthma

- Bronchial specimens post mortem or by bronchoscopy and biopsy in children 5-15 years
  - 7 nonasthmatics
  - 7 moderate asthmatics
  - 9 severe asthmatic

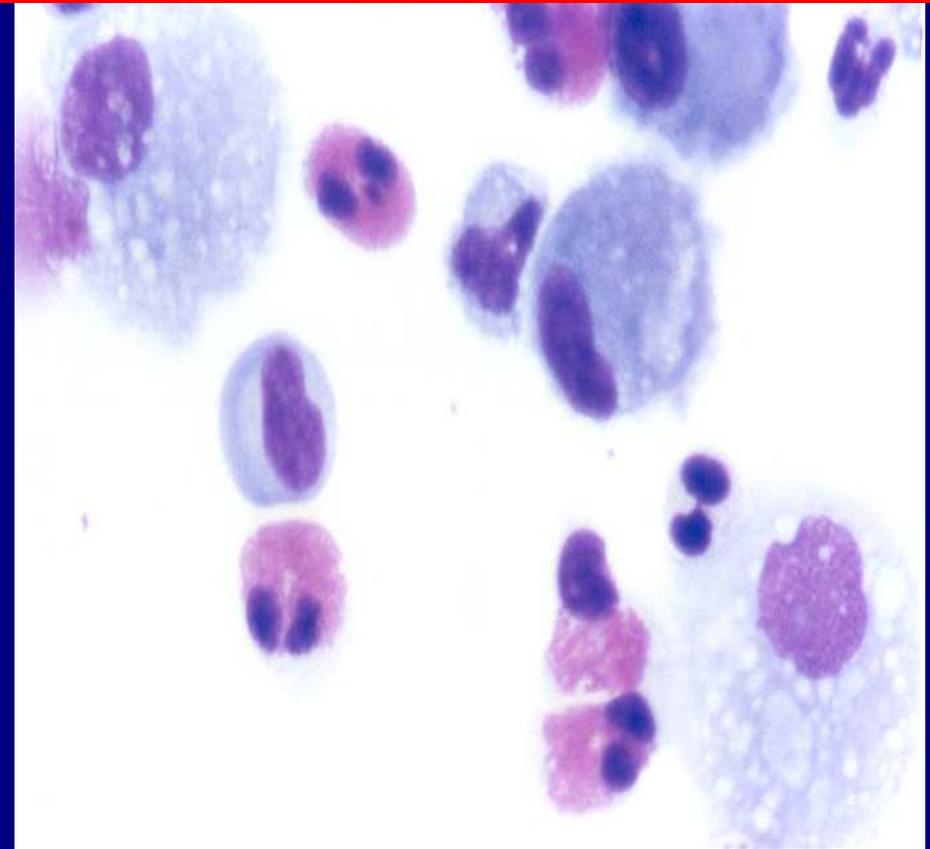
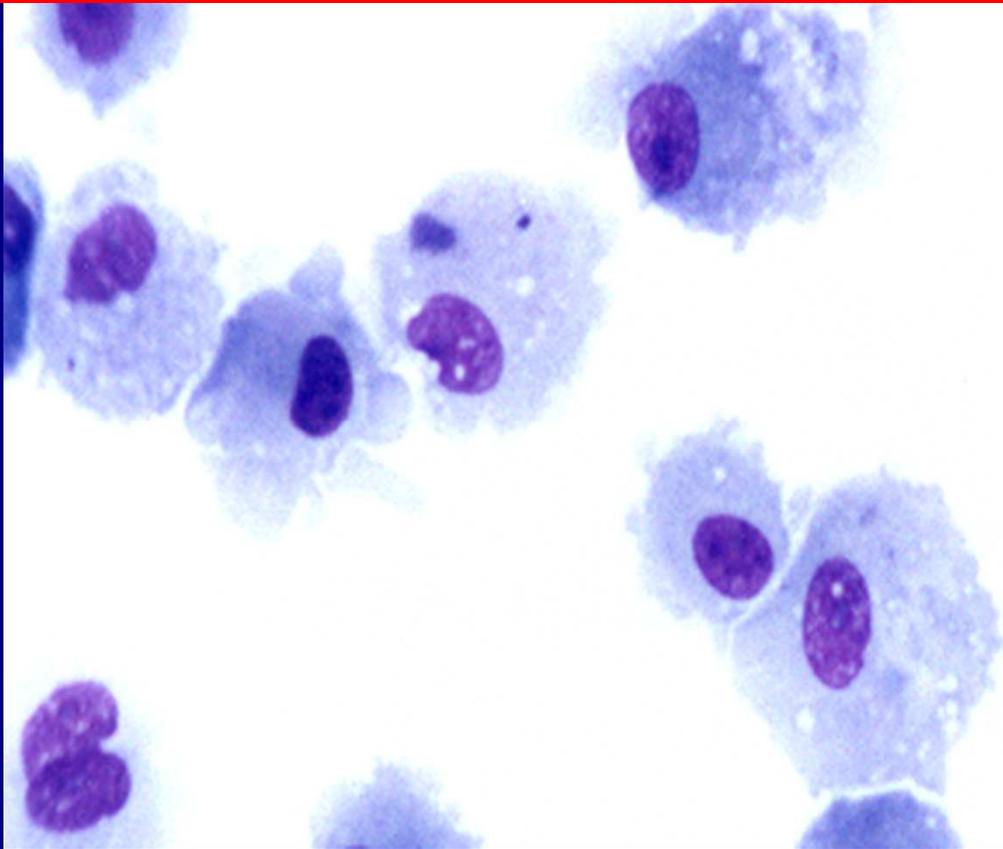


# Bronchoscopy and Bronchoalveolar Lavage



Stevenson EC et al. Clin.Exp.Allergy 27:1027, 1997

# BAL Cells 48 h After Allergen Challenge

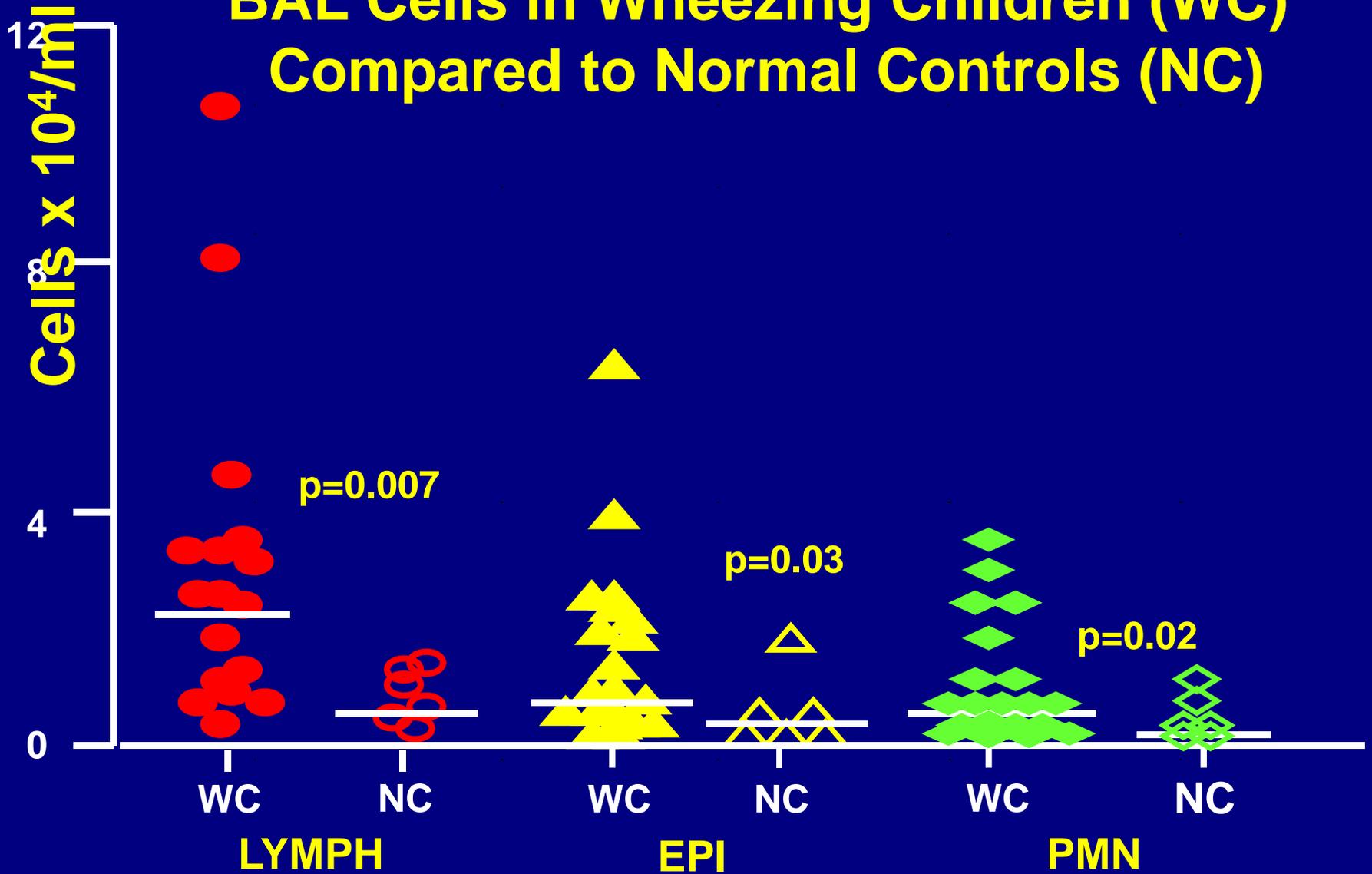


Laboratory of Drs. Jarjour and Kelly.

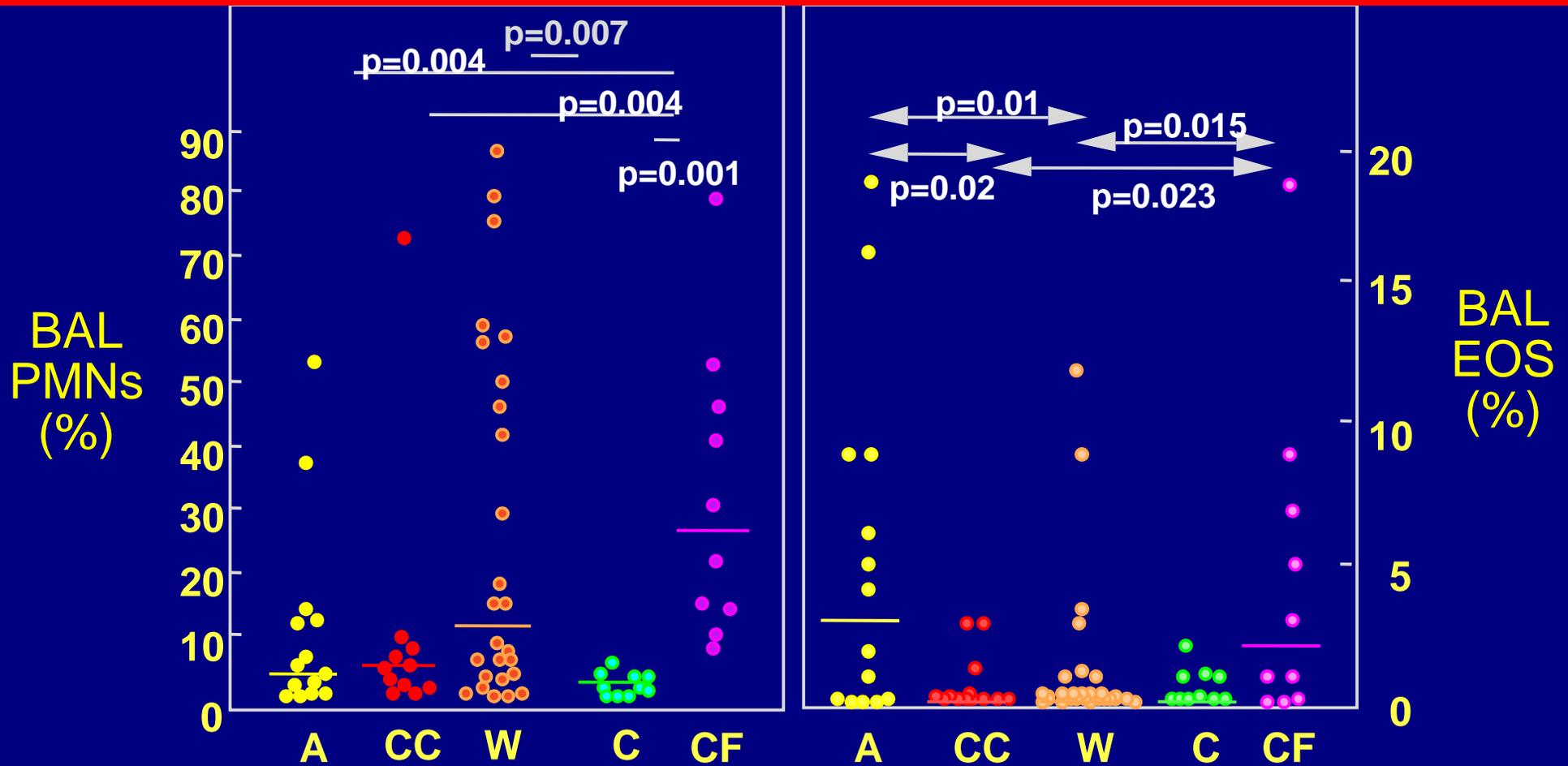
# Inflammation in Wheezing Infants

- **Infants and children < 60 mos with prolonged wheezing (> 2 mos within a 6 month period) not responding to conventional therapy**
  - Exclusion:
    - Acutely wheezing
    - > 450 µg/day of ICS
    - receiving antibiotics, oral steroids, or LTRAs within 1 mo of evaluation
- **BAL of right middle lobe**
- **Data on patients with + bacterial cultures or elevated LI was not included in the final analyses**

# BAL Cells in Wheezing Children (WC) Compared to Normal Controls (NC)



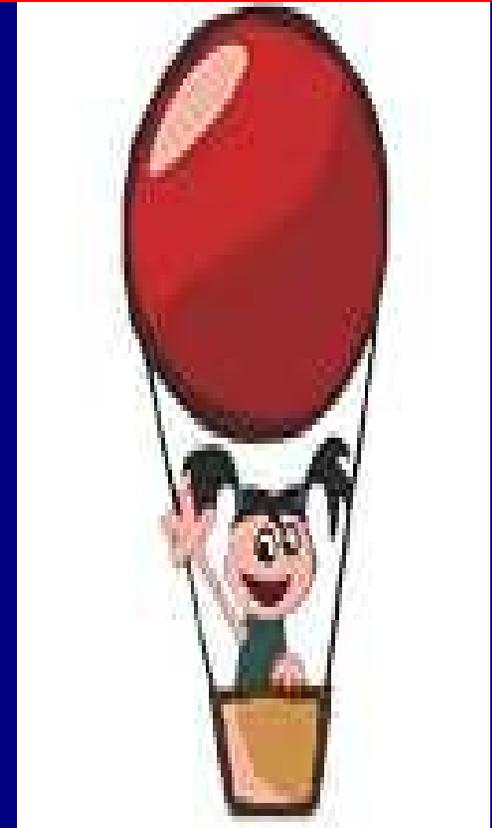
# Childhood Asthma is Characterized by AW Eosinophilia while Infantile Wheezing Characterized by AW Neutrophilia



Marguet; *AJRCCM* 159:1553, 1999



# Fractional Exhaled Nitric Oxide



**Niox MINO®**



# What is exhaled nitric oxide also known as the fractional exhaled nitric oxide (FeNO)?

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- Bronchial epithelium produces NO and its fraction in exhaled air
  - elevated in atopic asthma
  - a biomarker of eosinophilic allergic airway
  - FeNO is a biomarker which reacts rapidly in response to treatment or worsening of the disease
- Normal levels have now been established for children (20-25 ppb).
  - <20 ppb – unlikely to benefit from ICS therapy
  - 20-35ppb – may respond; evaluate in clinical context
  - >35 ppb – likely to response from ICS therapy

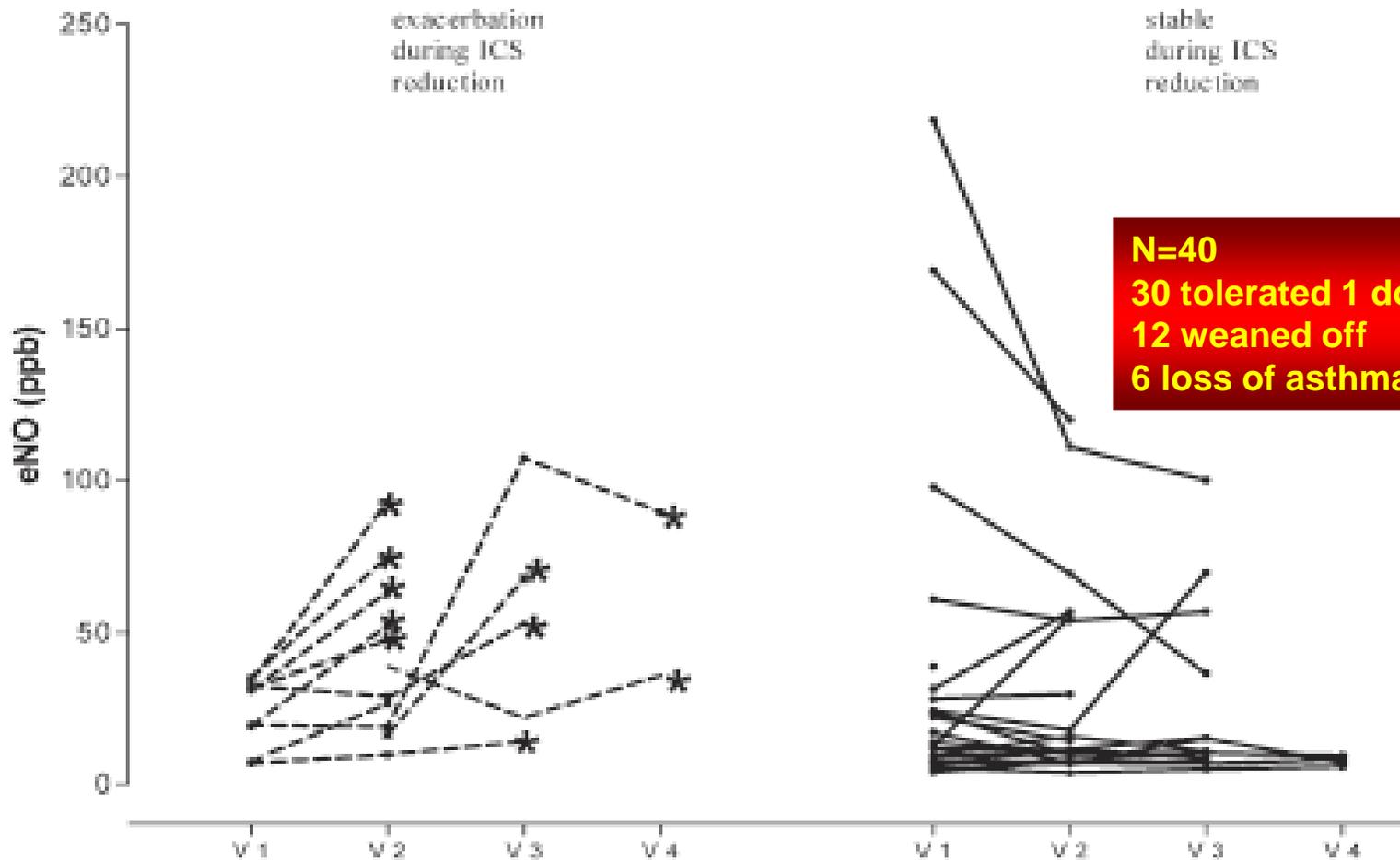


# Why is knowing the exhaled NO helpful in allergic asthma?

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- Measuring FeNO helps:
  - Identify steroid-responsive inflammation
  - Predicts and assess the patient's response to ICS anti-inflammatory therapy
  - May help optimize the dosage of ICS treatment
  - May help to predict loss of control and possible relapse therefore improving asthma outcomes
  - Helpful in monitoring compliance to ICS

# eNO as a Predictor of Asthma Exacerbation in Young Children during ICS Reduction



Zacharasiewicz A et al. *AJRCCM* 2005;171:1077-1082.

# eNO Off-Line Tidal Breathing Collection System



**Life would be infinitely happier if we could only be born at the age of eighty and gradually approach eighteen.....**

**Mark Twain**

